UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,267	02/07/2007	Gaetano Giammona	1108.1003	4701

20311 7590 01/25/2010

LUCAS & MERCANTI, LLP
475 PARK AVENUE SOUTH
15TH FLOOR
NEW YORK, NY 10016

EXAMINER
BROWE, DAVID

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
01/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/596,267	GIAMMONA ET AL.	
	Examiner	Art Unit	
	DAVID M. BROWE	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending.

Applicants timely submission of amendments and arguments on October 26, 2009 in response to the First Office Action on the Merits is acknowledged.

Withdrawal of Prior Objections

The abstract, specification, and claims 4 and 8-19 have been satisfactorily amended in response to objections presented in the first office action. Therefore, these objections are hereby withdrawn.

Withdrawal of Prior Claim Rejections – 35 USC § 103

Neither Bromberg *et al.*, Gupta *et al.*, Blum *et al.*, nor Giammona *et al.* disclose incorporating specifically propionyl L-carnitine, another alkanoyl L-carnitine, or a pharmaceutically acceptable salt thereof, into a cross-linked anionic hydrogel matrix, and administration of said matrix to a patient in need thereof for the treatment of ulcerative colitis, as presented in the newly amended claims now being fully examined on the merits. Therefore, the 35 U.S.C. §103 rejection presented in the first office action is hereby withdrawn. A new ground of rejection is presented herein below.

NEW GROUND OF REJECTION

Claim Rejections - 35 USC § 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-19 are directed to methods, but are incomplete as written for completely lacking essential steps. See MPEP § 2172.01. Therefore, one of ordinary skill in the art would not be apprised of the methods being claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bromberg *et al.* (U.S. Patent Application Pub. No. 2003/0152623), in view of Blum *et al.* (U.S. Patent No. 6,294,591), Giammona *et al.* (*Biochimica et Biophysica Acta 1428(1999): 29-38*), and Cavazza (U.S. Patent No. 6,013,670).

Applicant Claims

Applicants claim an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of polymers, derivatised with photo-cross-linkable groups, in the presence of acid comonomers. The polymer is α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA), or selected from the group consisting of polyaminoacid, polyaspartamide, acrylic or methacrylic acid, alkylvinyl, hydroxyalkyl cellulose, carboxyalkyl cellulose, polysaccharide, dextrin, pectin, amide and derivative, synthetic or natural rubber, and alginic acid polymers. The photo-cross-linkable groups are derived from the insertion of glycidyl methacrylate (GMA) and methacrylic anhydride (MA) in the side chain of PHEA; the acid comonomer is methacrylic acid or acrylic acid. The irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation. The matrix is preferably in the form of microparticles; and can also be in the form of nanoparticles, gels, films, cylinders, or sponges.

The matrix can contain one or more active ingredients and pharmaceutically acceptable excipients; and is for oral use. The excipients are selected from the group

consisting of bioadhesives, chitosans, polyacrylamides, natural or synthetic rubbers, and acrylic acid polymers. The active ingredient(s) is selected from the group consisting of analgesic agents, antitussive agents, bronchodilators, antipsychotics, antihypertensive agents and coronary dilators, selective 6-2 antagonists, calcium antagonists, anti-Parkinson agents, hormones, non-steroidal and steroidal anti-inflammatory agents, antihistamines, spasmolytics, anxiolytics, antidiabetic agents, cathartics, anti-epileptic agents, anti-cancer agents, disinfectants, sodium fluoride, cardioactive agents, and L-carnitine and/or alkanoyl L-carnitine or a pharmaceutically acceptable salt thereof. The alkanoyl L-carnitine is selected from the group consisting of acetyl, propionyl, butyryl, valeryl, and isovaleryl L-carnitine.

Applicants further claim a method of treating a patient or an animal in need thereof with the matrix composition, administered by the parenteral or vaginal routes; and a method for preparing a medicine with the composition for the treatment of cardiovascular, nervous system, intestinal and tumor diseases, wherein the intestinal disease is chronic ulcerative colitis or Crohn's disease, and the drug useful for the treatment of chronic intestinal disease is propionyl L-carnitine.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Bromberg *et al.* disclose an anionic hydrogel matrix obtained by cross-linking of polymers (Pg. 2, sec. 0012; Pg. 3, sec. 0013-0014; Pg. 4, sec. 0038; Pg. 5, secs. 0049-0052). The polymer is selected from the group consisting of polyaminoacid, polyaspartamide, acrylic or methacrylic acid, alkylvinyl, hydroxyalkyl cellulose, carboxyalkyl cellulose, polysaccharide, dextrin, pectin, amide and derivative, synthetic

or natural rubber, and alginic acid polymers (Pg. 5, secs. 0050, 0052). The matrix is preferably in the form of microparticles (Pg. 25, sec. 0193); can contain one or more active ingredients and pharmaceutically acceptable excipients; and is for oral use (Pg. 4, sec. 0039; Pg. 21, secs. 0137, 0144; Pg. 22, secs. 0145, 0147-0149, 0152-0154; Pg. 23, secs. 0171, 0180; Pg. 24, secs. 0182-0183). The excipients are selected from the group consisting of bioadhesives, chitosans, polyacrylamides, natural or synthetic rubbers, and acrylic acid polymers (Pg. 23, sec. 0180). The active ingredient(s) is selected from the group consisting of analgesic agents, antitussive agents, bronchodilators, antipsychotics, antihypertensive agents and coronary dilators, selective 6-2 antagonists, calcium antagonists, anti-Parkinson agents, hormones, non-steroidal and steroidal anti-inflammatory agents, antihistamines, spasmolytics, anxiolytics, antidiabetic agents, cathartics, anti-epileptic agents, anti-cancer agents, disinfectants, sodium fluoride, cardioactive agents, and L-carnitine and/or alkanoyl L-carnitine or a pharmaceutically acceptable salt thereof (Pg. 21, secs. 0137, 0144; Pg. 22, secs. 0145, 0147-0149, 0152-0154; Pg. 23, secs. 0171). Bromberg *et al.* further disclose a method of treating a patient or an animal in need thereof with the matrix composition; administered by the parenteral or vaginal routes; and a method for preparing a medicine with the composition for the treatment of cardiovascular, nervous system, intestinal and tumor diseases (Pg. 20, secs. 0134-0135; Pg. 21, secs. 0136, 0139-0142, 0144; Pg. 24, sec. 0184-0185).

Blum *et al.* disclose an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of acrylate or methacrylate copolymers, derivatised with photo-cross-

linkable groups, in the presence of acid comonomers (Col. 1, lns. 6-7, 12-18, 53-56, 63-67; Col. 2, lns. 1-3, 30-34; Col. 3, lns. 66-67; Col. 4, lns. 1-10, 22-23, 50-51). The photo-cross-linkable groups are derived from the insertion of glycidyl methacrylate (GMA) and methacrylic anhydride (MA) in the side chain of the polymers; the acid comonomer is methacrylic acid or acrylic acid (Col. 3, lns. 66-67; Col. 4, lns. 1-10). The irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation (Col. 2, lns. 4-13).

Giammona *et al.* disclose an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA) polymers, derivatised with photo-cross-linkable groups. The photo-cross-linkable groups are derived from the insertion of glycidyl methacrylate (GMA) in the side chain of the polymers; and the irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation.

Cavazza discloses the therapeutic use of alkanoyl L-carnitines and their pharmaceutically acceptable salts thereof in compositions for the treatment of ulcerative colitis (Col. 1, lns. 5-10, 54-56; Col. 2, lns. 2-9, 15-20). The alkanoyl L-carnitine is selected from the group consisting of acetyl, propionyl, butyryl, valeryl, and isovaleryl L-carnitine; the preferred alkanoyl L-carnitine is propionyl L-carnitine (Col. 2, lns. 2-9).

Ascertainment of the Difference Between the Scope of the Prior Art and the Claims (MPEP §2141.012)

Bromberg *et al.* disclose an anionic hydrogel matrix obtained by cross-linking of polymers; containing one or more active ingredients and pharmaceutically acceptable

excipients; for oral, parenteral, or vaginal administration for treating a patient or an animal in need thereof for cardiovascular, nervous system, intestinal and tumor diseases. Bromberg *et al.*, however, do not explicitly disclose that the cross-linking of polymers is achieved by beta-, gamma-, or UV-irradiation-mediated cross-linking of α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA) polymers, derivatised by insertion of glycidyl methacrylate (GMA) or methacrylic anhydride (MA), in the presence of acid comonomers; that the matrix specifically contains propionyl L-carnitine; and that the matrix is administered for the treatment of ulcerative colitis. These deficiencies are cured by the teachings of Blum *et al.*, Giammona *et al.*, and Cavazza.

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to combine the teachings of Bromberg *et al.*, Blum *et al.*, Giammona *et al.*, and Cavazza to devise applicants invention. Cross-linked polymer matrix synthesis traditionally required the use of toxic initiators and contaminating chemical cross-linking agents, often used unwanted or unpleasant solvent systems, and required additional laborious purification steps (Blum *et al.*, Col. 1, lns. 18-52; Giammona *et al.*); an approach not optimal for preparing products intended for medical or veterinary use. A skilled artisan, therefore, would be motivated to synthesize a stimulus-responsive hydrogel matrix for controlled-release drug delivery, as taught by Bromberg *et al.*, with the alternative approach to polymer cross-linking as taught by Blum *et al.*, using a polymer that is nontoxic and resistant to damage from the radiation

employed in the cross-linking procedure, such as PHEA as taught by Giammona *et al.*, with the reasonable expectation that this approach will successfully produce a more pure and safe product with less effort, as shown previously (Blum *et al.*; Giammona *et al.*).

Further, since Bromberg *et al.* disclose that an anionic hydrogel matrix obtained by cross-linking of polymers can contain a therapeutic agent or a pharmaceutically acceptable salt thereof, and be administered to a patient for the treatment of intestinal diseases, and since Cavazza teaches that propionyl L-carnitine or its pharmaceutically acceptable salt can be administered to a patient in a composition for the treatment of ulcerative colitis, one of ordinary skill in the art would be motivated to insert propionyl L-carnitine or its pharmaceutically acceptable salt into the cross-linked anionic hydrogel of Bromberg *et al.* with the reasonable expectation that this composition would successfully treat ulcerative colitis when administered to a patient in need thereof.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed October 26, 2009 have been fully considered but they are not persuasive. In claims 1-3 and 5-7, applicants claim a product-by process; wherein the product is essentially a cross-linked anionic hydrogel matrix comprised of α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA), or polymers selected from the group consisting of polyaminoacid, polyaspartamide, acrylic or methacrylic acid, alkylvinyl, hydroxyalkyl cellulose, carboxyalkyl cellulose, polysaccharide, dextrin, pectin, amide and derivative, synthetic or natural rubber, and alginic acid polymers; preferably in the form of microparticles. According to MPEP 2113, the patentability of a product-by-process claim is based on the product itself, and does not depend on its method of production. If the product in a product-by-process claim is the same as or obvious from a product in the prior art, the claim is unpatentable even though the prior art product was made by a different process. The Bromberg *et al.* reference alone essentially discloses a cross-linked anionic hydrogel matrix comprised of polymers selected from the group consisting of polyaminoacid, polyaspartamide, acrylic or methacrylic acid, alkylvinyl, hydroxyalkyl cellulose, carboxyalkyl cellulose, polysaccharide, dextrin, pectin, amide and derivative, synthetic or natural rubber, and alginic acid polymers; preferably in the form of microparticles. Thus, the Bromberg *et al.* reference discloses a product that appears to be substantially identical to applicants invention, and, therefore, according to MPEP 2113, the burden shifts to the applicant to show concrete evidence of an unobvious difference.

The fact that Bromberg *et al.* disclose incorporating "dangling chains of at least one amphiphilic copolymer" in the matrix is not a persuasive argument because: a) the "dangling chains of at least one amphiphilic copolymer" appears to be an *optional* component (see Pg. 3, secs. 0013-0015), and b) incorporating the “dangling chains” would not alter the fact that the product of Bromberg *et al.* would still essentially be a cross-linked anionic hydrogel matrix comprised of polymers selected from the group consisting of polyaminoacid, polyaspartamide, acrylic or methacrylic acid, alkylvinyl, hydroxyalkyl cellulose, carboxyalkyl cellulose, polysaccharide, dextrin, pectin, amide and derivative, synthetic or natural rubber, and alginic acid polymers; preferably in the form of microparticles.

Further, the combination of the Bromberg *et al.,* Blum *et al.*, and Giammona *et al.* references certainly does render obvious applicants claimed invention, even when all claimed limitations, including process limitations, are fully considered. Bromberg *et al.* disclose the anionic hydrogel matrix obtained by cross-linking of polymers; Blum *et al.* disclose an anionic hydrogel matrix obtained by applicants process: chemical reticulation by means of gamma-, beta-, or UV-irradiation of polymers suitably derivatized with photoreticulable groups, in the presence of methacrylic acid or acrylic acid comonomers; and Giammona *et al.* disclose an anionic hydrogel matrix obtained by means of gamma-, beta-, or UV-irradiation specifically of α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA) suitably derivatized with photoreticulable groups. The assertion that the §103 rejection from the first office action is inappropriate or deficient, because the Bromberg *et al.* and Giammona *et al.* references do not teach

irradiation of copolymers in the presence of acid comonomers, is not a persuasive argument since the Blum *et al.* reference clearly teaches a cross-linked matrix obtained by irradiation of anionic copolymers in the presence of methacrylic acid comonomers; a teaching very relevant to the instant application.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID M. BROWE whose telephone number is 571-270-1320. The examiner can normally be reached on Monday-Friday 7:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DAVID M. BROWE
Patent Examiner, Art Unit 1616

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616